GENOME
John Ohab
National Human Genome Research Institute
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Operator: Hello, and welcome to the Genome Sequencing Program Telebriefing, hosted by the National Human Genome Research Institute, part of the National Institutes of Health. Today's event will last for 60 minutes. There will be two principal speakers who have brief remarks, and then members of the media will be invited to ask questions. This call will be recorded and made available after 2:00 PM tomorrow on the National Human Genome Research Institute website, Genome.gov.

Now, we turn the program over to the moderator, Dr. John Ohab, Chief of the Communications and Public Liaison Branch at the National Human Genome Research Institute.

John Ohab: Good afternoon. I'm John Ohab, Chief of Communications at the National Human Genome Research Institute or NHGRI. I'd like to welcome you to today's telebriefing to discuss the next phase of NHGRI's Genome Sequencing Program.

First, I hope everyone online has a copy of the NHGRI news release covering today's announcement. It's now posted on our website, Genome.gov. We've also developed a resource page where you can find additional information about the Genome Sequencing Program, contact information for the research grantees' press offices, and links to several important documents.

We have several members of the NHGRI leadership group joining us today. We'll start with opening remarks from Dr. Eric Green, Director of the National Human Genome Research Institute; followed by Dr. Adam Felsenfeld, the program director who oversees the Genome Sequencing Program. Also, joining us from NHGRI are Dr. Lu Wang, the program director overseeing the Centers for Mendelian Genomics Program; Dr. Carolyn Hutter, a program director in the Genome Sequencing Program; and Dr. Jeff Schloss, Director of the Division of Genome Sciences.

I will turn things over to Dr. Green, followed by Dr. Felsenfeld, and then we'll open the discussion up with your questions. Dr. Green?

Eric Green: Thank you, John, and good afternoon, everyone. I really appreciate you joining us today.

We are at an extraordinarily exciting time for the field of genomics. Newer and better technologies are enabling researchers to more readily explore human genomes and at lower cost. The $1,000.00 human genome sequence [unfathomable] only a decade ago is now within our grasp and we're beginning to see real opportunities for using genomics in the clinic to improve human health. Already, oncologists are increasingly using DNA sequencing to examine the genomic make-up of tumors and, in some cases, pinpointing the key genomic alterations causing the disease, and new drugs targeting those alterations are gaining a foothold in cancer treatment.

NHGRI's flagship Genome Sequencing Program has played a pivotal role in these and other major genomic developments for the past quarter century. The program contributed the lion's share of the genome sequencing for the Human Genome Project and later spearheaded efforts

in comparative genomics that have helped us understand the genomes' working parts and in human genomic variation, yielding rich catalogs of differences among people's genomes such as by the recently completed 1,000 genomes project.

At a briefing not unlike this in 2011, we unveiled a new scientific plan for our Genome Sequencing Program that sharpened its focus on human disease and medical application. That effort contributed to a wide range of pioneering studies including those focused on rare diseases, common diseases, cancer, the clinical utility of genome sequencing, and the development of computational tools to facilitate genome sequencing. Overall, the past four years have seen our Genome Sequencing Program continue to be a driving force in advancing our ability to use genomics for understanding human disease and for improving medical care.

Today, we are here to discuss a new scientific plan for the NHGRI Genome Sequencing Program. This new plan will fund a set of genome sequencing centers whose research will focus on understanding the genomic bases of rare and common human diseases.

First, NHGRI will award approximately $240 million over the next four years along with co-funding from the National Heart, Lung, and Blood Institute to four institutions to establish the Centers for Common Disease Genomics. These centers will use large-scale genome sequencing to study how variation of the genome affects the risk for a range of common diseases such as heart disease, diabetes, and stroke.

As you know, common diseases affect hundreds of millions of people worldwide but they're also very difficult to study because they typically result from the complex interplay of genomics and environmental factors.

To address this challenge, the Centers for Common Disease Genomics plan to sequence between 150,000 and 200,000 genomes of individuals with a small group of disorders and, in doing so, the centers aim to develop better strategic approaches for using genome sequencing to study common diseases more broadly, giving better insights about how genomic differences among people influence disease risk.

Second, NHGRI will renew funding for a complementary effort, the Centers for Mendelian Genomics, which are focused on identifying the genomic causes of rare, inherited diseases. These disorders are typically caused by a genomic defect in a single gene. The new awards will total approximately $49 million for four years, including funding from the National Heart, Lung, and Blood Institute and the National Eye Institute. Of note, this is the second round of funding for this program.

Finally, our Genome Sequencing Program is establishing its first coordinating center to help organize data analyses, promote data sharing and collaborations, and provide other logistical support.

In summary, we believe that the time is right for the strategic deployment of very large-scale genome sequencing for unraveling the genomic bases of both rare and common diseases. Our efforts should teach us important lessons about how best to harness the power of genomics to study human diseases in new ways, while at the same time revealing important aspects about the genomic architecture of a wide range of human disorders so that scientists can study them more effectively.

Well, with that as a general overview, I will now turn things over to my colleague, Dr. Adam Felsenfeld, who will provide more details about the plans for these centers' programs. Adam?

Adam Felsenfeld: Thanks, Eric, and good afternoon, everyone.

In July of 2014, NHGRI hosted a workshop in Bethesda, which we worked with our research colleagues to formulate a new vision for the NHGRI sequencing program, one that will set the stage for future studies of common and rare diseases. As Dr. Green mentioned, the ability to generate whole genome sequence data costs approaching $1,000.00 per human genome, coupled with the availability of enough biological samples for studying common and complex diseases and similar resources for studying rare disease, the opportunity was clear.

Some months later, in a series of announcements, research was given the opportunity to apply for available funding. The applications were evaluated by peer review, and what were regarded as the best applications proposed excellent and diverse research plans for achieving the program's goals, including studying diverse types of disease using different project designs and developing new, ambitious approaches for implementing genome sequencing on a large scale. I look forward to working with these investigators both because I think they will be highly effective as consortium, and also because they have different ideas about how to pursue the program goals, which means that there'll be opportunities for really advancing the field.

I want to talk first about the Centers for Common Disease Genomics then a bit about the Centers for Mendelian Genomics. Dr. Green said common diseases like hypertension, diabetes, and some forms of mental illness affect hundreds of millions of people worldwide. Establishing the genomic contributions to these disorders is challenging because they result from a complex combination of interacting genomic variation and also environmental factors.

Now, there are several related challenges associated with understanding the genomics for common disease. The main ones have to do with how many different genomic variants are responsible and what types, how much of an effect each one actually has on disease risks – some can have large effects, some relatively minor – and how common those variants are in the population. Based on recent studies that have begun to identify genomic variants involved in common disease, we can expect that the answers to these questions might be different for different diseases. For some diseases, hundreds of variants might be important with each of which would have only a small effect. For others, the number of relevant variants may be much smaller. For some diseases, very small, single nucleotide changes might be important whereas for others, larger structural variants might be more important.

For some diseases, variants that are within protein coding regions, those that actually disrupt the protein, might be more important but for other diseases, variation in non-coding regions of the genome, areas that influence how and when genes are turned on or off, might be more important.

While we already have a great deal of information from previous studies to help us begin to answer these questions, there's much more to learn by studying these diseases in a systematic, comprehensive way. The work of these centers will be the starting point for new, more effective, and more efficient approaches for studying common disease. As the studies progress, the program will use the lessons it has learned to refine approaches and decide on which new diseases to study going forward.

As Dr. Green noted, researches at these centers will take a deep dive and in total examine between 150,000 to 200,000 human genomes over the

next four years to improve our understanding of how genomic variation contributes to common disease. Such large numbers are needed to allow for analyses that are statistically well powered to discover associations between variants and disease. In general, the plan study designs involve direct comparisons between genome sequences of people with the disease and those without. The centers will be studying a select group of disorders in order to develop approaches for using genome sequencing to study common disease more broadly. In other words, we need to pick good examples.

In addition to learning generalizable lessons, the program will also, as a result, implicate genomic variants in specific diseases, some that raise risk and others that may be protected. Finding both types of variants will be valuable information for the communities of researchers that focus on the specific diseases being studied. NHGRI plans to commit, assuming that funds continue to be available, $240 million over four years to four centers to study the genomic bases of common disease. Our partner institute, the National Heart, Lung, and Blood Institute, is also contributing funding support.

The newly established centers will be located at the Broad Institute in Cambridge, Massachusetts; Washington University in St. Louis; Baylor College of Medicine in Houston; and the New York Genome Center in New York City.

I'll now turn to the Centers for Mendelian Genomics Program. As Eric said, NHGRI is renewing support for this program as well. To draw simplified contrasts between the common disease and the rare Mendelian diseases, the latter are caused by individually rare variants that are rare in the population that have large effects. In other words, the presence of

those variants results in a very high chance of getting the disease. Many Mendelian diseases are serious and as each individual disease is rare collectively, they affect many families.

The Centers for Mendelian Genomics will use genome sequencing to search for the causes of as many Mendelian diseases as possible. There are approximately 7,400 known Mendelian diseases. We still do not know the genomic bases for more than 3,000 of these. During the previous funding period, the Centers were extraordinarily successful, finding more than 700 genes that likely cause Mendelian disease. Going forward, we expect that success to continue.

For the Centers for Mendelian Genomics Program, NHGRI is also partnering with the National Heart, Lung and Blood Institute, and as well the National Eye Institute to provide approximately $49 million over four years, assuming funds remain available, to four centers located at the Broad Institute in Cambridge, Massachusetts; Yale University in New Haven, Connecticut; the University of Washington in Seattle; and a combined site involving the Baylor College of Medicine in Houston and John Hopkins University in Baltimore.

Because of the scope, scale, and complexity of the NHGRI Genome Sequencing Program, NHGRI has also decided to fund the coordinating center at Rutgers University in New Brunswick, New Jersey to support the coordination and collaboration among the other centers and to guide outreach activities. In addition, the coordinating center will play a key scientific role by improving data availability and leading a variety of data analysis efforts. We plan to support the coordinating center for about $4 million over four years.

With that, I think we're ready to take any questions.

John Ohab: This is John Ohab again. At this time, we'll open up the briefing to your questions. Before you ask your question, please remember to tell us who you are and the name of the organization.

Operator: At this time, if you would like to ask a question, please press the * and 1 on your touchtone telephone. You may withdraw your question at any time by pressing the # key. Once again, if you would like to ask a question today, please press the * and 1 on your touchtone phone.

We'll take our first question from Michelle Munz with St. Louis Post. Your line is open.

Michelle Munz: Hi. I was wondering if you could please comment more on why these four institutions were chosen, and I'm particularly talking about the common disease study, how they've been able to position themselves to be at the forefront of this effort. With me being from St. Louis, I would love anything you could say in particular about Washington University.

Adam Felsenfeld: Sure. Of these four centers, three were actually also awarded in the previous iteration of the Genome Sequencing Program the Large-Scale Sequencing and Analysis Centers Program which ended in November. All three have a very productive history. They have undertaken many projects with funding from very diverse sources. They have altogether worked on lowering costs and they'll have excellent track records in lowering costs. They all have excellent track records of producing very high quality data, and they all have excellent histories of providing intellectual contributions into how to tackle the scientific problems that are the focus of our programs and the focus of other programs.

Now, it wasn't just us who chose them, of course. There was an independent peer review. We asked generically for this program, four centers for proposals that would address a series of goals. That RFA is published and I'm pleased to send it to you or John can send it to you if you don't already have a link to it. It makes very clear what we ask for and we ask the peer reviewers to evaluate those proposals towards those program goals. These four proposals were the successful ones that apply.

Eric Green: This is Eric Green. The other comment I would just add is there was nothing unusual done here. This is fairly standard NIH approach for funding bodies of research that NIH wants to fund. As Adam mentioned, this went through an advisory process that led to a formal request for applications – that's what an RFA is – that people respond to that and then they submit grant applications. Those are reviewed by a peer review process and then go through a standard advisory process that was nothing different than what has been going on at NIH for decades.

In this particular case, we have a lot of experience with operating a large Centers program. By the way, this has started with the Human Genome Project and continues to the present time, and so this was pretty much following that framework for soliciting applications, reviewing applications, and making decisions.

Adam Felsenfeld: We have historically done that approximately every four to five years for the program, and have had at some times more participants and sometimes fewer.

Michelle Munz: Okay. Thank you.

Operator: Thank you. We'll move next to Durrie Bouscaren with St. Louis Public Radio. Your line is open.

Durrie Bouscaren: Hi. Can you hear me?

John Ohab: Yes.

Durrie Bouscaren: Okay, great. My question is the idea of isolating risk genes has been sometimes controversial, so I was wondering in moving from putting such a large investment towards finding new risk genes for common diseases, are there any ethical implications you guys were looking at in trying to control for when authorizing this?

Eric Green: This is Eric Green. Let me make a couple of comments. First of all, the terminology "risk genes" – we're really looking for our spellings in our DNA that are conferring a greater or lesser risk for diseases and sometimes those fall within genes and sometimes those don't but by and large, we're taking a very open-ended look to figure out what the spelling differences are and eventually those will be linked to genes.

With regard to thinking about in particular the ethical issues, we always think about that. As an institute and as a field, I think it's a distinguishing characteristic of the field of genomics since its inception a little over 25 years ago to always be thinking about the implications for society, including ethical and legal implications for this work. To be honest with you, I don't think this kind of work is necessarily more concerning at all, to be honest with you, in part because the kind of information that could come out of this is overwhelmingly medically important. We believe that when you think about some of the disorders that are going to be tackled by this program going forward or similar programs have tackled diseases like autism and Alzheimer's and diabetes and so forth, the health burden associated worldwide with these disorders that is so immense that any progress we could make in unraveling the underlying causes of those

diseases has potential to have a huge impact in a very positive way for the future of understanding these diseases and managing these diseases. Certainly, we want to think about some of the ethical implications but I think the medical consequence of this is so compelling that it really is what drives us more than anything.

Adam Felsenfeld: I'm going to answer this in a different way because I heard a slightly different question embedded in there, and that is that we do take great care because we are sequencing DNA from research participants and we want to make sure that the sequence data and the phenotype data can be available for the research community to do additional studies and to do larger meta-analyses, anything that they can unleash their creativity on towards these goals.

We are very careful to make sure that the samples that are used are properly consented. For us, the ideal kind of consent makes it clear that the samples will be used broadly for biomedical research. The data itself is deposited in a way that only authorized investigators who apply to get it can get permission to get the data directly for specific research studies, and their purposes have to be consistent with what the consent stipulated.

Durrie Bouscaren: Okay, thank you. Can I ask one follow-up question, too?

John Ohab: Please.

Durrie Bouscaren: Okay, cool. You guys touched on this earlier but the idea – I feel like earlier with sequencing cancer genome, people were able to compare a person's genetic – their healthy genome and then the genome of the cancer. With these illnesses, that's not necessarily the case. For you guys, why this initiative now and why this level of investment? Is it going to be enough?

Adam Felsenfeld: Yes. Those are great questions. Exactly for the reason that you mentioned, in cancer which is itself a very difficult problem, at least you have the advantage of comparing a tumor to normal DNA, so cells from the same individual. Any differences are more likely to be signal. They're not guaranteed. There's still a lot of noise but it's an easier comparison. There are fewer differences.

When you compare between two unrelated people, it's very hard to tell what's important and that's one of the reasons why such large sample numbers, people usually think in terms of such large sample numbers. In fact, the range of scientific opinion on this is pretty wide. Some people think that especially in order to detect signals in non-coding regions of the genome where you can't easily assign function that you might need as many as 100,000 cases and controls for one of these diseases to really exhaust all of the variants that are likely to make a significant contribution at all to disease to find them all.

That is certainly one way to think about it but there are other ways. There are other possible designs. There are family designs that are appropriate in some cases. There are extreme designs that are appropriate in some cases that can reduce numbers. You can also design studies that look instead of disease phenotypes that look at what we call endophenotypes which, for example, one might be cholesterol level, something that's easily measured the same way between people, and it can be a good proxy and that could proxy for the actual disease phenotype and that can boost power and enable you to get answers with fewer samples, though it has disadvantages as well. All of these really important scientific issues that are central to this program are wrapped up in the answer to your question.

Eric Green: The other aspect to consider because I also heard you asking why are we doing this now, I think the key thing is that it was not affordable four years ago. What drives our ability to do this kind of audacious scale now is the technological advances that we have seen in DNA sequencing that, as I said in my opening remarks, are inching us closer to the $1,000.00 human genome threshold and we will cross that threshold. With that kind of a price tag, it means studies that were once unimaginable because of their scale are now quite possible.

Adam Felsenfeld: Yet another kind of answer is we're pretty sure that many communities that are interested in specific diseases are going to undertake these and they're going to undertake them individually which is extremely important that they do it, but any early information and systematically generated information that can be put out as early as possible will be helpful in guiding what will be done next in a useful way.

Carolyn Hutter: This is Carolyn Hutter. I'm a program director at NHGRI. I think embedded in your question, too, was the really important question about what is the comparator and the controls in this case. It is moving from the studies of somatic variations in cancer to looking at risk, and so it really builds on a lot of epidemiological principles of this idea of comparing people with disease to people without disease.

Also, one of the reasons to do this now and to think about it there has also been a lot of work and thinking, and one of the challenges that this program is taking on is the question of how to really make those comparator groups and are there ways to maximize and think about how we're doing that in smart ways so that we can share comparison groups between different disease types and other approaches that will also help with the efficiency and really allow us to really answer this fundamental

question about genetic variation that's associated with who gets disease and who doesn't.

Durrie Bouscaren: All right. Thank you so much.

Operator: Thank you. All right. Now, we'll move to Christie Rizk with GenomeWeb. Your line is open.

Christie Rizk: Hello. I have two questions. The first one, I was wondering if you could tell us, are there any more details on what you're hoping to achieve with the Mendelian diseases project? Specifically, I know you said you wanted to sequence between 150,000, 200,000 genomes with the rare disease project, and I was wondering if there were any similar goals or statistics you could give us for the Mendelian disease program.

My second question is diseases influenced by so many things other than genome in the environment - the microbiome, proteomics, pharmacogenomics, etcetera. I was wondering if there are any plans to – the grants in the rare disease or Mendelian disease programs involve all of those aspects, or are there plans to later on merge the data that those grants are getting with research from other universities or centers?

Eric Green: Sure. Lu Wang will take the first question.

Lu Wang: Yes. I'll take the first. This is Lu Wang. To answer your first question, I will just briefly mention what the Mendelian Centers have achieved so far. They have sequenced over 20,000 whole exomes and that led to the discovery of more than 1,600 genes that underlie several hundred Mendelian diseases. About half of those genes are novel in the sense that they had not been implicated in human disease before. In the process of making these discoveries, the Centers have innovated their discovery

pipelines in order to increase the success rate and they have done a good job disseminating the product and the tools. They have also reached out to the community to coordinate and to enable possible collaborations to be established.

Given what they have achieved, seeing the continuing trend of the discovery of novel causal genes and because the discovery of causal genes from sequencing to finalizing the analysis is a scalable process, this program will focus on finding as many novel causal genes as possible in the next four years and will continue to improve the discovery pipelines and disseminate the tools they have developed and will continue to reach out to the community to help coordinations to be established.

As far as the range of numbers of the diseases that [funding] centers will tackle and the causal genes they may discover, given what they have achieved so far and the observed complexity of what seemed to be simple, rare disease mechanisms, the goal is to discover more than 1,000 causal genes with more than half of them being novel. The causal genes, I expected to be responsible for a comparable number of Mendelian diseases.

Adam Felsenfeld: Just to recall your question, you asked about gene by environment interactions and maybe epigenomics and microbiome?

Christie Rizk: Right, exactly.

Adam Felsenfeld: Right. Primarily, this program is going to be about finding genome variation. Where there are samples, where environmental data have been collected, they will be used that way. Those variables will be included in analyses, but this program is relying on existing large sample sets funded under other auspices and sometimes they have that data and sometimes

they don't. There are even fewer samples that have already been collected that have good microbiome data that's very intensive to get it right and reproducible. For now, the answer is no.

One of the nice things about the way this program is structured is that it's very hooked into the communities that are working intensively on the diseases being studied. It's one of the things we look for in thinking about samples because those communities are certainly going to take those samples farther. Whether it's gathering other omic data or adding more phenotype data or additional genotyping, we certainly hope that that happens and if the data that we generate are very high quality and compelling, we think that that will happen rapidly.

Christie Rizk: Thank you.

Operator: Thank you. We'll move now to Sharon Begley with STAT. Your line is open.

Sharon Begley: Hi, everyone, and thank you for doing this. Dr. Green, could you just clarify what are the 150,000 to 200,000 individual genomes that will be sequenced? Are those of people [at risk of] one or another disorder and so a comfortable number has to be sequenced of people without that target disease?

Eric Green: I'm going to forward that question over to Adam Felsenfeld who's much more involved in the study design aspects of this program.

Adam Felsenfeld: Right, and thank you. The answer is that total has to include both cases and controls. As Carolyn mentioned, we hope to leverage controls. We hope to find a way to have a set of common controls. There are other large studies that we hope to collaborate with that are going to also be

sequencing some samples with similar phenotypes that haven't been assessed and those can be controlled. Although the total number of […] cases and comparisons, it's not necessarily going to be a one-to-one and it may be different for different studies.

Sharon Begley: Right. Thank you.

Operator: As a reminder, if you'd like to ask a question today, please press the * and 1 on your touchtone phone. We'll take a follow-up question from Michelle Munz with St. Louis Post. Your line is open.

Michelle Munz: Hi, again. Yes, so I'm wondering given how these diseases are so complex with all these different genes possibly involved and lifestyle factors, how risky is this research? How certain are you that you will find something that is meaningful and can improve care for people?

Eric Green: This is Eric Green. I can take the first pass but I welcome my colleagues to weigh in on that as well. The honest truth is we don't know what we don't know. This is part of a nature of exploratory work. We don't really know the complete answer for any complex disease, any common disease we're talking about. Boy, if we at least had an answer for one, we'd have some framework for really understanding how many genomic variants we're talking about, what the relative contributions of environment and lifestyle and genomics that play into that disorder. There are some studies that are giving us clues based on that you could try to model and extrapolate to think you're going to know what are some of the general underlying architecture is going to be, but we don't know it for certain.

We should be clear that this is still exploratory work by nature. It's one of the reasons I would stress why we are not instantly tackling 20 different – I could name very quickly 20 compelling common diseases that we'd want

to do, but we're not doing it that way. We're not even going to tackle 10 because we believe the reason we're going to go very deep with a handful of disorders is we believe it's going to require that kind of comprehensiveness, that kind of systematic approach to really understand a few and from that, we will finally be in a position to see what the answer is, at least for the first few diseases, and then model what will be needed and predict better what will be needed going forward for other diseases.

I don't think we should lead you to believe that we have the perfect formula for completely getting all the genomic information about common diseases, even for a given disease. This is still research and there's a lot unknown, and we believe though, based on lots of early evidence and based on a lot of very important modeling that has been done, that this is going to give us tremendous insights but I wouldn't promise comprehensive insights.

Adam, do you want to add anything to that?

Adam Felsenfeld: Yes. To answer another way, I'm very confident that we will get some very interesting hits and some may be quite valuable because previous studies have shown, but really understanding what it takes to complete the task, to reach the point of diminishing returns, that's an answer that's very important to have early. I also want to say that there are other deliverables that are not necessarily for specific diseases. Here, there's knowhow about how to apply sequencing. There's further cost reduction. There is just having a very high quality and available data set of whole genome sequence data for thousands and thousands of people so that people who do analysis can unleash their creativity on it and really understand how to get the most out of it. That itself will be an important resource, so there's many other things.

Finally, another kind of answer is that even though there are plenty of diseases with significant environmental effects, sometimes finding the genomic contributions can give you good clues about the environmental effects. If you end up hitting an estrogen receptor or some other pathway that interfaces with the environment, you have a really good clue of where to look for environmental causes.

These things all play off of each other. This is an important chunk. I think no scientific effort, however large, can be considered as an island that we hope this interacts with lots of other parallel efforts.

Michelle Munz: Could I ask another question?

Eric Green: Sure.

Michelle Munz: Okay. I was hoping you could comment more about the seemingly impossible trajectory of how just over 10 years ago it took you $1 billion and over a decade to map the first human genome, and here we are about to map 200,000 genomes to find answers to these complex diseases. Did you ever just imagine that it would get at this point so quickly?

Eric Green: It didn't happen by accident. It wasn't just coincidental that there were remarkable advances in technology. Sitting in the room is another NHGRI senior leader, Jeff Schloss, who has for many years been the director of our genome sequencing technology program of which the $1,000.00 genome technology development effort was part of. I'm going to let him answer this question.

Jeff Schloss: My first comment is yes, isn't it cool? It's amazing. NHGRI has been dedicated to in parallel with implementing the technologies as quickly as we've been able to do to also seeing to it that we're not stuck on a given

set of technologies but always looking for better, cheaper, faster ways to implement these kinds of studies. That has been central to our goals and the institution has dedicated a lot of money to it. Our advisors have always been very supportive of that.

We really see these activities going hand in hand. There's a highly original research going on by people with, in some cases, thought to be crazy ideas about new ways to do sequencing. Those people are working in parallel with people who have much more conservative ways to improve sequencing and they're all feeding off of each other. To the extent then that we learn from those kinds of studies, that new information is snapped up very rapidly by companies, because many of our grantees are academic and they don't have the ability to convert that knowledge into really highly useful tools. The new information is snapped up very quickly by companies who do know how to do that and, of course, they have to invest a lot more funds than what we've invested very often to convert those into platforms that can be used by investigators such as those in the genome centers to actually produce these data. The insight is then cycled back from the sequencing centers who really do know how to implement these new technologies back to the companies and, frankly, back to the innovators. It's an interesting and useful cycle of activities that we just try to keep them all integrated with each other so that we continue to get the kinds of innovations that make programs like the GSP possible.

Eric Green: I would add to that, as it relates to an earlier question of by no means being certain that even the sequencing of 150,000 to 200,000 will be sufficient for X number of diseases. We are imagining the possibility that even bigger studies are going to be needed to untangle certain common

disorders and other diseases of medical interest. A $1,000 genome may simply not be cheap enough for being able to afford even yet larger studies which is why the institute remains committed to having a thriving technology development program, not letting up on the accelerator because we think there's more innovation to be had. It's not relevant for the program we're announcing today but let me just say the institute continues to be committed to technology development in the arena of DNA sequencing.

Michelle Munz: Thank you, and I'm so sorry. I missed the first speaker's name.

Eric Green: Jeff Schloss.

Michelle Munz: Okay. Thank you.

Operator: Thank you. It appears we have no further questions at this time. We'll turn the call back to Dr. John Ohab for any closing remarks today.

John Ohab: If there are no questions, then this concludes today's telebriefing. I wanted to thank those of you still on the line as well as everyone here in the room today for taking the time to be part of this discussion of the next phase of the NHGRI's Genome Sequencing Program.

If you have any follow-up questions, please contact Steven Benowitz at steven.benowitz@nih.gov and we'll be sure to get you some more information. Also, please visit our website for more resources.

Thank you very much.

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